

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Amar Lulla, <i>et al.</i>	§	
	§	Group Art Unit: 1616
Serial No.: 10/518,016	§	
	§	Examiner: Kristie Latrice Brooks
Filed: July 6, 2005	§	
	§	Confirmation No.: 4912
For: COMBINATION OF AZELASTINE AND	§	
STERIODS	§	

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

1. I am a co-inventor of the invention claimed in the above-identified patent application.

2. Attached as Exhibit A is comparison data for five compositions:

Column 1: Azelastine.HCl
 Column 2: Budesonide
 Column 3: Azelastine.HCl & Budesonide
 Column 4: Fluticasone Propionate
 Column 5: Azelastine.HCl and Fluticasone Propionate

Table I of Exhibit A sets for the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone

propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

3. Attached as Exhibit B is a compilation of statements from 6 medical practitioners, labeled B1-B6, along with typed transcriptions. As is self-evident, these statements attest to various advantages and superior results associated with patient use of the DUONASE product comprising azelastine and fluticasone.

4. A pharmaceutical formulation comprising azelastine and fluticasone is commercially available where approved as DUONASE nasal spray, as shown in attached Exhibit C containing information from the following website:

<http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=213>.

5. I am unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

6. The present application is licensed to Meda Pharmaceuticals.

7. I, Geena Malhotra, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Date: 3rd July 2009,

Geena Malhotra
Name: GEENA MALHOTRA

Exhibit A, Table I: Comparative Composition data of Azelastine with steroids

Ingredients	Azelastin (%w/w)	Budesonide (%w/w)	Azelastine+B udesonide (%w/w)	Fluticasone (%w/w)	Aze+Flu (%w/w)
Drugs	137 mcg	64 mcg	137+64 mcg	50 mcg	140+50 mcg
MCC+CMC (Avicel RC)	-	-	2.0	0.75	2.0
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	2.5	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3	-	2.3
Polysorbate 80	-	0.016	0.005	0.0025	0.005
BKC 10% w/v solution	0.125	-	0.005	100 ml	0.10
Phenyl ethyl alcohol	-	-	-	0.125	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01	-	0.01
Sodium Chloride	0.68	-	-	-	-
Citrate Monohydrate	0.048	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid	-	q.s.	-	-	-

Exhibit A, Table II: Comparative Stability data of Azelastine with steroid Compositions

Stability tests	Azelastine	Budesonide	Azelastine + Budesonide	Fluticasone	Azelastine + Fluticasone
	INITIAL	INITIAL	INITIAL	INITIAL	INITIAL
Assay	100	97.6	98+97	101.6	100+101.12
pH	6.78	4.51	6.0	6.4	6.1
Total Impurity	0.03	0.26	2.32+0.11	0.52	0.6
	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M	25/60 RH at 1M
pH	6.86	4.68	5.94	Not Done	Not Done
Total Impurity	0.12	0.25	0.97 + 0.07	Not Done	Not Done
	25/60 RH at 3 M	25/60 RH at 3 M	25/60 RH at 3 M	25/60 RH at 3 M	30/65 RH at 1M
pH	6.76	4.6	5.96	6.21	5.85
Total Impurity	0.13	0.42	5.39+0.16	0.46	0.84
	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M	40/75 RH at 1M
pH	6.86	4.69	5.92	6.35	5.82
Total Impurity	0.13	0.29	5.53+0.05	0.52	0.89
	40/75 RH at 3 M	40/75 RH at 3 M	40/75 RH at 3 M	40/75 RH at 3 M	40/75 RH at 3 M
pH	6.76	4.61	5.91	5.98	5.81
Total Impurity	0.18	0.49	18.29+0.23	0.53	0.85

Exhibit B1

Dr. C.M. Mathew Chooracken

B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.

Senior Specialist in E.N.T.

Civil Surgeon

District Hospital, Kottayam

Reg. No. 9473

Consultation:

Behind Margin Free Market

Near Kottayam East Police Station

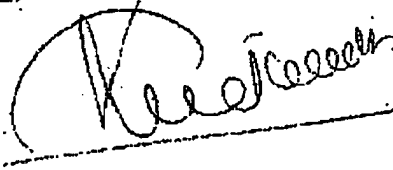
Collectorate P.O., Kottayam - 686 002

Ph: 2564884, Mb: 9447288822

To Cepla Respiratory L

I have been using
the Deconase nasal spray
regularly for many nasal allergy
patients. I found it is
very effective when compared
to the available other nasal
sprays. Oral medications
can be avoided as well.

Kottayam
23/2/05-


Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E. N. T.
Civil Surgeon,
District Hospital, Kottayam
Reg. No. 9473



Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

I have been using the Duonase nasal spray regularly for my nasal allergic patients. I found it is very effective when compared the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Exhibit B2

Confidential

डॉ. पी.एन. तेजनकर

एम. एस. (ई.एन.टी.)

नाक, कान, गला एवं गर्दन रोग विशेषज्ञ
पूर्व रजिस्ट्रार ई.एन.टी. हॉस्पिटल, नागपूर

क्लिनिक

गुजराती समाज, नई सड़क, उज्जैन
☎ 2561981

समय प्रांत: 11 से 2.00

जय मेडिकल सेन्टर (वसावडा पेट्रोल पम्प के पास)
घंटाघर, फ्रिगेज, उज्जैन ☎ 2514884

रविवार अवकाश

समय सायं 6 से 8.30

विशेषज्ञ

- नाक एवं सायनस इन्डोलॉजी (दूरबीन द्वारा आपरेशन) • माइक्रोलेरिन्जियल सर्जरी
- माइक्रोड्रम सर्जरी (जर्मनी, फ्रांस एवं स्वीट्जरलैण्ड से प्रशिक्षण प्राप्त) • नाक की प्लास्टिक सर्जरी (राईनोप्लास्टी)

Regarding Deconase

18.8.2008

Using this product - for last 80 many days

This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy. A

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)

• Antagonism to H₁ receptor activity & few side effect.

- Acts on multiple receptors

The systemic bio-availability is less so can be used for a longer period without side effect.

Tough to allergy Safe to H₁ receptors

Dr

DR.P.N.TEJANKAR

M.S. (E.N.T)
E.N.T and Neck Specialist
Ex-Registrar E.N.T. Hospital, Bombay

Gujrati Samaj,
Nai Sadak, Ujjain
☎ 2561981

Time Mor: 11 to 2.00

CLINIC

Jai Medical Centre (Near
Vasavda petrol pump)
Ghantaghar, Freegunj, Ujjain
☎ 2514884

Time: eve. 6 to 8.30

SUNDAY HOLIDAY

Specialist

• Nose and sinus endoscopy • Microlaryngeal Surgery • Microear Surgery (Trained from Germany, France and Switzerland) • Plastic Surgery of the Nose (rhinoplasty)

Regarding Duonase

Using this product for last so many days. This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy.

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)
- Antagonises the H1 receptor activity with few side effect.
- Acts on multiple symptoms.
- The systemic bioavailability is less so can be used for a longer period without side effect.

Tough to allergy safe to Nose

Confidential

डॉ. प्रसाद रा. जवळेकर एम.एस. (इ. एन. टी.)

रजि. सं. ०८१८८२

(कॉन्-11क-कसा)

कृष्णा जनरल हॉस्पिटल

धनवंतरी फात, नाक, घसा हॉस्पिटल

गव्हाण नैलडॉन, पी. सी. एम. टी. चौक, भोसरी,

ओशन रोड, नाशिक

फुणे ४१२०३२. फ़ोन २८५२९५१६

ता. जुन्नर, जि. पुणे, ४१०

वेळ: संध्या. ५.०० ते ८-०० वा.

रविवार बंद

०२०३२ - (हॉस्पि.) २४४०६६, मि २४३३

Date. 2.7.8.05

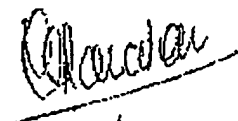
I have prescribed "bunase Nasal Spray for 258 patients since Aug 2004 to Aug 2005. And I found that a bunase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "seasonal allergic rhinitis." Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both in "bunase Nasal Spray."

So I hereby strongly recommend bunase Nasal Spray for allergic rhinitis.

डॉ. प्रसाद रा. जवळेकर

रजि. सं. ०८१८८२

कृष्णा जनरल हॉस्पिटल, गव्हाण नैलडॉन, पी. सी. एम. टी. चौक, भोसरी, फुणे ४१२०३२.



DR. PRASAD JAWALEKAR M.S (E.N.T)

Reg.no.071882

Krishna General Hospital

Gavhane building, P.C.M.T Chowk,

Bhosari, Pune 411039. ☎ 27129516

Time: eve. 5-00 to 8-00

SUNDAY CLOSED ☎02132-(Hosp.)244766 (R)243969

E.N.T Specialist

Dhanvantari E.N.T.Hospital

Khodad Road, Narayangaon,

Taluka Junnar, Dist. Pune 410504

I have prescribed "Duonase Nasal spray" for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "Duonase Nasal Spray".

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

Confidential

No. 25409



Dr. Manish Munjal

M.B.B.S., M.S. Diplomate of National Board (ENT), M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., D.M.S.

ENT - ROSE - THROAT AND HEAD-NECK SURGEON

Ph.: 2300182

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Consultant Otorhinolaryngology & Head-Neck Services
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and Brown Hospital, Ludhiana.

Office-cum-Residence
52-C, Udhham Singh Nagar,
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Next to Lions Bhawan, Ludhiana.

To

By

To

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Pr

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Web.

Exp.

Jill

I have been using nasal sprays from
The year 1993, ever since I joined my
Present institution. I have used beclomethasone,
budesonide, Azelastine, fluticasone,
mometasone, with oral antihistamines
down the line till date.

The present combination spray of a weak
(non sedating component) Azelastine and
fluticasone (steroidal component) is Comp
by itself in my patients of Chronic
Simple rhinitis; following nasal & sinus
Polyps surgery and those unwilling
for surgery or unfit for surgery.

There is a response noted within a week
Δ in a few patients but the maximum

Consultations: Evening 2.30 P.M. to 3.00 P.M. 5.30 P.M. to 5.50 P.M.

Emergency & off-hours visits only: Evening: 5.30 to 8.00 P.M.

www.munjial.com

Confidential

Number of patients respond very well after three weeks of therapy.

Recurrences of polypsis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed as noted with earlier preparations is not noted to that much extent of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing a fungal pathology. (Though have not found much literature on this issue on the net)

The combination therapy (Deoxyso) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one picks up some contraindication or side effect.

DR. MANISH MUNJAL

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.

The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

There is a response noted within a week in a few patients but the maximum number of patients respond very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed as noted with earlier preparations is not noted to that much extent of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing and fungal pathology (though have not found much literature on the issue on the net).

The combination Therapy (DUONASE) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some contra indication or side effect of this indication.

Exhibit B5



VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)

698/5, Yamuna Vihar Road, (Road No. 55), Majpur, Delhi-110053

: 229111
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: 229111

Dr. Sunesh Vats

M.B.B.S., M.S. (ENT)
CONSULTANT EAR, NOSE & THROAT SURGEON
Formerly ENT Surgeon
ST. STEPHEN'S HOSPITAL
LNJP & GB PANT HOSPITAL

डॉ० सुरेश वत्स

एम.बी.बी.एस., एम.एस. (ई.एन.टी.)

कान, नाक व गला रोग विशेषज्ञ एवं सर्जन
समय : सुबह 10 से 1 तक शाम 6 से 8 तक

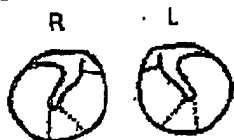
Relatuable Yes/No. S. No. (रविवार अवकाश)

Name Age & Sex Resi. Date At

रक्तिय को सेवल Audiometry एवं Speech Therapy
रवि. सुब. सुब. सुब. 10 से 1 तक शाम 6 से 8 तक
P.T. Audiogram/Hearing Assessment
Aided Audiogram
Hearing Aid Trial
Speech Assessment
Speech Therapy
Cochlear Test
Impedance

Hb T.C. B.C. S.T. C.T.
ESR, Mar-Tess
Blood Sugar R.F.-Sp. Blood Urea
Urea R.F. & M/S
Prothrombin Time Platelets Count
HbA1c, HbV (I & II)
AEC I/E. Nasal smear for Eosinophils
VDRL. ASLO Titre
T3 T4 TSH
Cytology smear for AFP
Throat/Mucosa/Ear/Nostril Q & S
Stom. - m/s & o/s
FNAC

X-Ray Mastoid - 1 st. Oblique (BR) Towne
X-Ray PNS - Waters
X-Ray Naso-Pharyngo-nasal Tissues (Sarnath)
X-Ray Neck soft Tissues - Lateral
X-Ray Cervical Spine - Lat. & A.P.
X-Ray - Styloid Process (Bilateral)
X-Ray Occlusal view for pt mouth
X-Ray - Submandibular region - Lat. St. - U.
X-Ray - Internal Auditory Meatus
X-Ray - T.M. Joint Lat. Open & closed Jaw
X-Ray - Nasal Bones - Lateral
X-Ray Skull - AP - Lateral
X-Ray - Chest P.A. View
Barium Swallow
C.T. Scan - PNS - Coronal 3 mm cuts
C.T. Scan - Temporal bones
C.T. Scan - Neck - Head
E.C.G.



Rinne's
Weber's

I/L Exa.:



Right

Left



Nasal spray
is unique & distinct for
from available nasal spray
due to it- Combined Ant
allergic & antinflammatory
properties. It is an exel
product, effective in the
of Allergies & Allergic
Rhinitis with or with
Corticosteroids - Budesonide

Allergy: Worth trying to
use in certain patients &
oral antihistamine may be better

17/8/08
Dr. SURESH VATS
M.S. (ENT)
Sr. CONSULTANT EAR, NOSE &
THROAT SURGEON
Reg. No. MCI-2108, DMC-1712
69B/5, Road No. 66, Mayapuri, Delhi-53

Dr. SURESH VATS

Duonase Nasal spray is unique & distinct from other available nasal sprays due to its combined Anti-allergic & anti-inflammatory properties. It is an excellent product, effective in majority of patients with allergic Rhinitis with or without concomitant Bronchial Allergy. Worth Trying. Safe to use in certain patients where oral antihistamine may be harmful.

डॉ. बी. बी. माथुर
एम.डी.

Dr. B. B. Mathur
M.D.

वरिष्ठ विशेषज्ञ एवं एसोसिएट प्रोफेसर
चेष्ट एवं टी.बी. विभाग
सरदार पटेल मेडिकल कॉलेज, बीकानेर
RMC No. 7458

Senior Consultant & Associate Professor
Chest & T.B., Hospital
S.P. Medical College, BIKANER
☎ Hos. : 0151-2226333, Res. 0151-2528789

Ref No.

Date... 17/8/05

Duonase Nasal Spray is highly effective
in controlling symptoms and subsequent relapse in
patients of Allergic Rhinitis. I have used
this product in many patients and due to
its efficacy it gives confidence to patients &
it takes care of symptoms due to rapid onset of
action and long lasting relief due to anti-
inflammatory action.

डॉ. बी. बी. माथुर
एसोसिएट प्रोफेसर
सी. सी. एवं चेस्ट विभाग
सरदार पटेल मेडिकल कॉलेज
बीकानेर (राज.)

Dr. B.B. MATHUR

Duonase Nasal spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients as it takes care of symptoms due to rapid onset of action and long lasting relief due to anti-inflammatory action.



📁 Essential Cipla 🔍 Essential Tools 😊 Leisure Time

Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

Each spray delivers

Azelastine hydrochloride BP 140 mcg

Fluticasone propionate BP 50 mcg

Composition

Fluticasone propionate BP 0.0357% w/v

Azelastine Hydrochloride BP 0.10% w/v

Benzalkonium Chloride NF 0.01% w/v

(as preservative)

Phenyl Ethyl alcohol USP 0.25% v/v

(as preservative)

Description

Duonase is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a second generation H₁ receptor antagonist with potent topical activity and fluticasone propionate, synthetic corticosteroid with anti-inflammatory properties.

Pharmacology

As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properties of both the molecules are given separately.

Pharmacology of Azelastine Hydrochloride

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H₁-receptor antagonist activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H₁-receptor antagonist activity.

Pharmacokinetics and Metabolism

After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (C_{max}) are achieved in 2-3 hours. Following intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized to its principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythromycin failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimetidine (400 mg twice daily), a nonspecific P450 inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.

The major active metabolite, desmethylazelastine, was not measurable (below assay limit) after single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing of azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine were

from 20-50% of azelastine concentrations. When azelastine hydrochloride is administered, desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranasal oral route.

Pharmacology of Fluticasone Propionate

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to natural hormone. However, the clinical significance of these findings in relation to the low levels is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics:

Absorption: Fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (10 pg/mL) only when recommended doses were exceeded and then only in occasional samples. Low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral administration of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91%, with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,050 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had 1/2,000th the affinity (approximately 1/2,000) of the parent drug for the glucocorticoid receptor of human cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Indications

Duonase is indicated for the management of symptoms of allergic rhinitis once the need for an antihistamine and corticosteroid has been established. It is recommended to treat **moderate to severe persistent symptoms** in adults above 12 years. For children above 5 years, **Duonase** is recommended for **severe symptoms** of allergic rhinitis. **Duonase** can also be used for treating non-allergic vasomotor rhinitis in adults and children 12 years of age and older.

Dosage And Method of Administration

Adults and children 5 years and older: 1 spray/nostril twice daily

The recommended dosage should not be exceeded. Not recommended for use in children under 5 years.

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Contraindications

Duonase is contraindicated in patients with or known hypersensitivity to azelastine hydrochloride or fluticasone propionate or any of the components of the preparation.

Warnings and Precautions

- Concurrent use of this combination with alcohol or other CNS depressants or other antihistamines should be avoided as additional reductions in alertness and additional impairment of CNS performance may occur due to azelastine.
- The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience symptoms of withdrawal e.g. joint and/or muscular pain, lassitude and depression.
- The concomitant use of an intranasal corticosteroid with other corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the hypothalamic-pituitary-adrenal axis. Therefore the combination should be used cautiously in patients with other pathological conditions requiring steroids.
- Intranasal corticosteroids may cause a reduction in growth velocity when administered at a higher dose. The recommended dosage of **Duonase** should not be exceeded.
- Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections. Chicken pox and measles for example can have a more serious and even a fatal course in children on immunosuppressant corticosteroids.
- During long term therapy, monitoring of hematological and adrenal function is advised.
- In clinical studies with intranasal fluticasone propionate, the development of local infections of the nose and the pharynx with *Candida albicans* has been seen rarely; if such an infection develops, it may require treatment with appropriate local therapy. Discontinuation of the treatment with **Duonase** is advised.

Drug Interactions

The use of **Duonase** in patients taking concurrent drugs, which are potent inhibitors of the cytochrome 450 3A4 system eg. Ketoconazole and protease inhibitors such as ritonavir may be associated with increased systemic exposure of fluticasone.

Pregnancy

The combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in human milk. Hence, caution should be exercised while prescribing this combination to nursing mothers.

Undesirable Effects

The most likely side effects with this combination are headache, somnolence, pharyngitis, epistaxis, nasal burning/irritation, nausea, vomiting, cough, taste disturbance. The combination may produce a bitter taste, which may lead to occasional nausea. Bitter taste disappears sometime.

Shelf Life

2 years

Storage and Handling Instructions

Store below 30 °C.
 Do not refrigerate.
 Protect from direct sunlight.

Packaging Information

Duonase Nasal Spray
 Sales pack contains 70 metered doses

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